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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/026,276	02/19/98	KENTEN J	IGN-9601

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EXAMINER	
HAMUD, F	
ART UNIT	**PAPER NUMBER**
1646	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No. 09/026,276	Applicant(s) KENTEN et al
	Examiner Fozia Hamud	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Oct 29, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *2-19, 21-40, 42-57, 59-75, and 81-83* is/are pending in the application.

Of the above, claim(s) *9-12, 28-32, 37, 48-52, and 65-69* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *2-8, 13-19, 21-27, 33-36, 38-40, 42-47, 53-57, 59-64, 70-75, and 81-83* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 1, 20, 41 and 58 have been canceled, and claims 5, 6, 16, 24, 25, 36, 42, , 46, 56, 59, 62, 63, 74, 75, 81, 82 and 83 have been amended in Paper No.13, filed on 10/29/99. Upon further consideration claims 9-12, 28-32, 37, 48-52, 57, 65-69 are withdrawn from consideration by the examiner, as they are drawn to non-elected species. Thus claims 2-8, 13-27, 33-47, 53-64, 70-75 and 81-83 are pending and under consideration by the Examiner.

2. Receipt of Applicant's arguments and amendments filed in Paper No.13, 10/29/99 is acknowledged.

3. The following previous rejections and objections are withdrawn in light of Applicants amendments filed in Paper No.13, 10/29/99:

(I) The rejection of claims 1-14, 16-34, 36-54, 56-71, 73-75 and 81 made under 35 U.S.C. §112, first paragraph.

(ii) The rejection of claims 1-6, 8, 15-16, 22-25, 27-35, 37-38, 41, 43-46, 48, 50-55, 57-58, 60-63, 65-68, 71-73 made under 35 U.S.C. §112, second paragraph.

(iii) The rejection of claims 1, 41 and 58, made under 35 U.S.C. §102(b), as being anticipated by Lussow et al (1991).

(iv) The rejection of claims 2-3, 8, 14, 42-43, 54, 59, 60, made under 35 U.S.C. §102(e), as being anticipated by Viestra et al (US Patent 5,851,791).

(v) The rejection of claims 10, 13, 28, 33, 37, 50, 53, 67 and 70, made under 35 U.S.C. §102(b), as being anticipated by Mouristen et al (March 1995).

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Applicant's arguments filed in Paper No.13, filed on 10/29/99, have been fully considered and were deemed persuasive in part. The issues remaining are restated below.

Claim Rejections-35 USC § 103

6. The rejection of claims 15, 35, 55, 72, 81 and 83, made under 35 U.S.C. 103(a), as being unpatentable over Van der zee et al in view of Vannier et al, is maintained for reasons of record set forth in pages 10-12, in Paper No:8, filed on April 26,1999.

Applicants argue that Vannier et al lacks information regarding the construction of the ubiquitin fusion protein because the researchers make no reference as to the construction of the fusion protein or why it was used. This argument is not persuasive, because the procedures for producing ubiquitin fusion proteins, as claimed in the instant Application, were within the ability of one of average skill in the art at the time the instant invention was made and the Vannier et al reference published. Production of ubiquitin fusion proteins are routine, as Applicants have argued else where, (see the argument traversing claim rejection under 112, first paragraph on pages 7-10 of Applicants''s response filed on 10/29/99 in Paper No:13). Vannier et al immunized Balb/c mice with four subcutaneous injections of purified ubiquitin-hFSHR fusion protein (Ub-hFSHR), isolated hybridomas secreting antibodies against Ub-hFSHR and purified said antibodies, (page 1359, column 2, second paragraph). As to the question, why was the Ub-hFSHR disclosed in Vannier et al reference used, it was used to elicit immune response against the hFSHR part of the fusion protein. Therefore, the

ubiquitin fusion protein of the instant Application would have been obvious to one of ordinary skill in the art upon reading the Vannier et al reference.

Claim rejections-35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2-8, 13-19, 21-27, 33-36, 38-40, 42-47, 53-56, 5964, 71-75 and 81-83 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7a. Regarding claims 2, 21, 42 and 59, the phrase "characterized"renders the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

7b. Claim 83 recites "....., the ubiquitin moiety being modified such that the ubiquitin is non-cleavable...", however, it is not clear exactly how and where is the ubiquitin moiety modified, is the modification on the N-terminal or the C-terminal amino acid of ubiquitin moiety? Is there an insertion, substitution or deletion of certain amino acid residues to avoid said cleavage? Appropriate correction is required.

Claim rejections-35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

> *(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.*

8. Claims 2-3, 8, 13, 27, 42-43, 53, 70, 74-75, are rejected under 35 U.S.C *§ 102*(e) as being anticipated by Rechsteiner et al (US Patent 5,763,225).

Rechsteiner et al teach the synthesis and recovery of ubiquitin-carboxy extension peptides wherein the peptides contain two to forty amino acid residues, (see abstract, and claims, especially claim 1). Rechsteiner et al disclose that the ubiquitin fusion proteins of their invention may be isolated and purified without cleavage of the peptide, and may be possible to obtain anti-peptide antibodies by immunizing with the ubiquitin-carboxyl terminal directly cross linked to a suitable carrier, (see column 8, lines 52-57). The present invention is directed to a ubiquitin fusion protein fused to a single epitope-containing segment, said segment comprising two or more identical epitopes, the fusion protein being characterized by the ability to stimulate an immune response to the heterologous epitope contained therein, at a fusion site selected from the N-terminus, the C-terminus or an internal fusion site. Therefore, the ubiquitin fusion proteins taught by Rechsteiner et al reference anticipates instant claims 2-3, 8, 13, 27, 42-43, 53, 70, 74-75.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> *(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

9. Claims 2-3, 8, 13, 27, 42-43, 53, 70, 74-75, are rejected under 35 U.S.C *§ 102(b)* as being anticipated by Wittliff et al (1990).

Wittliff et al teach the expression and characterization of an active human estrogen receptor as a ubiquitin fusion protein from *E.coli*, (see abstract, and page 22017, column 1). Wittliff et al disclose that the estrogen receptor expressed as ubiquitin fusion protein behaves identically as the wild-type receptor in ligand binding and DNA binding properties and is recognized by monoclonal antibodies directed against two different epitopes of the human estrogen receptor, (page 22017, column 1, second paragraph). Wittliff et al teach that the expression of proteins as ubiquitin fusion facilitates stabilization and increases efficiency of translation, and that the attachment of ubiquitin promotes proper folding, thus preserving the proteins biological activity, (page 22019, column 2). The present invention is directed to a ubiquitin fusion protein fused to a single epitope-containing segment, said segment comprising two or more identical epitopes, the fusion protein being characterized by the ability to stimulate an immune response to the heterologous epitope contained therein, at a fusion site selected from the N-terminus, the C-terminus or an internal fusion site. Therefore, the ubiquitin fusion proteins taught by Wittliff et al reference anticipates instant claims 2-3, 8, 13, 27, 42-43, 53, 70, 74-75.

9b. Claims 2-3, 8, 13, 27, 42-43, 53, 70, 74-75, are rejected under 35 U.S.C *§ 102(b)* as being anticipated by Vannier et al (1996).

Vannier et al teach the expression of the extracellular domain of human follicle stimulating hormone receptor (hFSHR) in E.coli as a ubiquitin fusion protein, (see abstract). Vannier et al disclose that the immunization of mice with Ub-hFSHR allowed the preparation of high affinity anti-

receptor monoclonal antibodies, this Ub-hFSHR fusion protein also provoked the formation of anti-receptor antibodies in monkeys, (page 1359, column 2, second paragraph and page 1365, last paragraph). The Ub-hFSHR disclosed by Vannier et al meets all the limitations in instant claims 2-3, 8, 13, 27, 42-43, 53, 70, 74-75.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 4-7, 14-19, 21-26, 33-36, 38-40, 44-47, 54-56, 59-64, 71-73 and 81-83 are rejected under U.S.C. § 103 as being unpatentable over Wittliff et al in view of Van der Zee et al (1995).

The teachings of Wittliff et al have been set forth directly above in section 3a of this office action, however, Wittliff et al do not disclose a fusion protein comprising two ubiquitin peptides as claimed in instant claims 4-6, 23-25, 44-46, 61-63, or a ubiquitin fusion protein that is posttranslationally modified by the addition of fatty acids to enhance immunogenicity, or a ubiquitin fusion protein comprising gonadotropin releasing hormone epitopes, or ubiquitin fusion proteins comprising non-contiguous epitope containing segments..

Van der zee et al teach a fusion protein comprising a gonadotropin releasing hormone (GnRH), fused to fimbriae by means of recombinant DNA technology, for the development of contraceptive vaccine for domestic animals, (see abstract and figure 4 on page 757). Van der zee et al disclose that GnRH is one of the most attractive vaccine components for immunoneutralization because it is regarded as the key regulatory peptide that controls reproduction in mammals, (page 753, column 1). The researchers describe the construction of a fusion protein by inserting the nucleotide encoding GnRH in hyper variable regions of the subunit gene of P-fimbriae of E.coli, generating hybrid GnRH-fimbriae, which were expressed efficiently on the cell surface of E.coli, (page 754, column 2, last paragraph). Vaccination of female rats and young bull calves with the GnRH containing fimbriae induces not only a serological but also a considerable pharmacological effects, (page 757, lines 23-26). Van der zee et al demonstrate that GnRH is a promising candidate for the development of a new contraceptive vaccine.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention, to modify the GnRH fusion protein taught by Van der zee, by generating GnRH as a ubiquitin fusion protein, using the teachings of Wittliff et al, because Wittliff et al teach that the expression of proteins as ubiquitin fusions facilitates stabilization and increases efficiency of translation, and that the attachment of ubiquitin promotes proper folding, thus preserving the protein's biological activity, (page 22019, column 2). Also, ubiquitin is a small highly conserved self protein that is found in all eukaryotic cells and that does not induce immune response in animals.

With respect to claims 4-6, 23-25, 44-46, 61-63 directed to a ubiquitin fusion protein comprising two ubiquitin peptides flanked either side of the desired peptide or protein, it would have been

obvious to one of ordinary skill in the art to generate such a fusion protein, because upon cleaving one of the ubiquitin moieties, the resulting protein is still part of a ubiquitin fusion and therefore, would be expected to be more stable than the protein alone.

With respect to claims drawn to ubiquitin fusion proteins that are posttranslationally modified by the addition of fatty acids to enhance immunogenicity, it is well known in the art that making such modification is desirous since it results in the enhancement of immunogenicity.

With respect to claims directed to ubiquitin fusion proteins comprising non-contiguous epitope containing segments, it would be obvious to attach more than one of epitope in a non-contiguous fusion to ubiquitin, since such attachment would be expected to increase the chance of the epitope being recognized by the immune surveillance, and thus enhancing the stimulation of an immune response to said epitope.

With respect to claims drawn to the attachment of the desired epitope to the N-terminus of ubiquitin, it is irrelevant where ubiquitin is attached, since fusing proteins with ubiquitin, would be expected to generate a highly stable ubiquitin fusion protein, only if the N-terminus of the desired protein is necessary for it's activity, would the attachment of ubiquitin to the protein's N-terminus create a problem.

With respect to claims directed to modifying the ubiquitin moiety to avoid cleavage, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to make such modification, to avoid cleaving the ubiquitin moiety from the fusion, since expressing proteins as ubiquitin fusions, results in stable, properly folded, biologically active proteins.

One of ordinary skill in the art would be motivated to generate GnRH-ubiquitin fusion hormone because Van deer zee et al teach that GnRH plays a central role in the regulation of reproductive functions in vertebrates and that it is a promising candidate for vaccine component. Van deer zee et al also teach that there is a demand for an effective and low cost means of fertility control of domestic animals.

Conclusion

11. No claim is allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit1646
January 18, 2000

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER